CPC COMBINATION PRODUCTS COALITION

Combination Products Update

AHLA Life Sciences Institute

October 16, 2009

Bradley Merrill Thompson

General Counsel

Combination Products Coalition

CPC COMBINATION PRODUCTS COALITION

Topic

1. **Who we are**
2. Public health importance of combo products
3. The industry's needs for guidance
4. GMP Proposed Rule
5. Post-market Safety Reporting Proposed Rule
6. Priorities going forward

CPC COMBINATION PRODUCTS COALITION

CPC: Purpose

- To clarify and streamline the regulatory paradigm for combination products
- While protecting the public health

CPC COMBINATION PRODUCTS COALITION

Membership

- Up to 20 drug, device and biologics companies have engaged in CPC activities. Some members include:
  - Abbott
  - Baxter
  - Becton Dickinson
  - Genentech
  - Pfizer
  - Roche Diagnostics
- Most active participants are regulatory affairs professionals for member companies.
- Diversity of industry representation is encouraged.

CPC COMBINATION PRODUCTS COALITION

Current Activities

- Partnering with RAPS to host policy summit on GMP proposed rule (more later) and webcast on adverse event proposed rule, during comment period.
- Developing comments on both proposed rules
- Shepherding a clinical trials proposed guidance
- Comments re adverse events and GMP proposed rules
- Legislative work

CPC COMBINATION PRODUCTS COALITION

CPC Draft Clinical Trial Guidance

- Feb. 27, 2009, CPC filed draft guidance, *FAQs on Pre-Clinical and Clinical Research on Combination Products*
- Sept. 22, 2009, submitted revised version structured as amendment to 2006 FDA guidance, *Early Development Considerations for Innovative Combination Products*
- Developed in response to industry's desire for guidance in this area
- Topics addressed include:
  - IND and IDE submissions
  - Clinical study design
  - Safety reporting issues
  - Issues pertaining to specific technologies
- Working with FDA to identify the best way to move forward

CPC COMBINATION PRODUCTS COALITION

Draft Injector Guidance

- FDA released draft injector guidance on April 27, 2009 - *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*
- Comments submitted by July 27, 2009
- In 18-page comments, CPC expressed some significant concerns
  - Could *significantly increase* burden for certain injectors, for example stand-alone device injectors and simpler types of injectors
  - Potential inconsistencies with existing device guidance (e.g., piston syringe guidance)
- Very interested in the pathway document

CPC COMBINATION PRODUCTS COALITION

Topic

1. Who we are
2. **Public health importance of combo products**
3. The industry's needs for guidance
4. GMP Proposed Rule
5. Post-market Safety Reporting Proposed Rule
6. Priorities going forward

CPC COMBINATION PRODUCTS COALITION

Public Health Importance

- Combination product technology enables safer and more effective technologies
  - local administration and
  - individualized therapy
- Can avoid certain systemic effects and toxicities
- Utilize some of the most cutting-edge scientific technologies
  - nanotechnology,
  - genomics,
  - molecular diagnostics,
  - tissue engineering,
  - stem cell research,
  - and more.

Examples

- Magnetic nanoscopic probes.
- A miniscule device put in the eye to provide controlled and sustained release of a variety of drug compounds.
- A small hand-held device that allows drugs to be easily inhaled.
- Small drug-eluting stents implanted into airways as a minimally-invasive treatment option for emphysema.
- Using autologous stem cell therapy and a delivery device to treat cardiovascular disease.
- A metal device packed with bone growth material that fosters natural bone regeneration.
- Light-activated drugs (photosensitizers) administered by IV injection.

CPC COMBINATION PRODUCTS COALITION

Industry Growing

- In 2005, the combination products market was estimated at $6.4 billion and expected to reach $11.4 billion by 2010.
- Some sources estimate that 30% of new products under development are combination products
- As of mid-2006, 130 nanotech-based drugs and delivery systems and 125 devices or diagnostic tests were in preclinical, clinical or commercial development
- U.S. National Science Foundation has predicated that nanotechnology will produce half of the pharmaceutical industry product line for 2015
- US demand for nanomedicines was forecasted to expand annually by 17%, reaching
  - $43 billion in 2012 and
  - $85 billion by 2017

CPC COMBINATION PRODUCTS COALITION

Impact on OCP

- With essentially static resources, OCP has
  - Maintained timeliness so far
  - Preserved a sense of openness and transparency
  - Kept the operational trains moving
- But that will be increasingly difficult to accomplish, at the same time meeting industry's need for guidance

CPC COMBINATION PRODUCTS COALITION

Topic

1. Who we are
2. Public health importance of combo products
3. **The industry's needs for guidance**
4. GMP Proposed Rule
5. Post-market Safety Reporting Proposed Rule
6. Priorities going forward

CPC COMBINATION PRODUCTS COALITION

Guidance-Needs Survey

- Goals
  - Evaluate current industry concerns and priorities
  - Communicate these to FDA
  - Inform CPC policy agenda

FDA U.S. Food and Drug Administration — U.S. Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

Office of Combination Products

Overview of the Office of Combination Products

Definition of a Combination Product

Frequently Asked Questions

Product Jurisdiction/Assignment of Combination Products:

Final Rule: Definition of the Primary Mode of Action of a Combination Product -*Federal Register* [PDF 4.91MB] *(August 25, 2005)*

- Guidance for Industry and FDA Staff: How to Write a Request for Designation (RFD) [PDF 79KB] *(August 2005)*
- Assignment of Combination Products/Product Jurisdiction Program - Final Rule *(June 23, 2003)*
- Jurisdictional Updates
  - Jurisdictional Update: Breath Test Combination Products *(September 2006)*

Requests for Comments

- Review of Agreements, Guidances, and Practices in Compliance with the Medical Device User Fee and Modernization Act of 2002 [PDF 72KB] *(September 2006)*
- Request for Comments:
  - Adverse Event Reporting
  - Number of Marketing Applications for Combination Products *(September 2005)*

Guidance Documents and Procedures

- Guidance for Industry and FDA Staff: Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) *(July 2007)*
- Minimal Manipulation of Structural Tissue [PDF 49KB] *(September 2006)*
- Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products [PDF 130KB] *(September 2006)*
- Plans for Proposed Rulemaking on Good Manufacturing Practice and

What's New

- Recent Examples of Combination Product Approvals

Contact Us

We are interested in your comments and suggestions about combination products issues. Please contact:

Thinh Nguyen MS., Director
Office of Combination Products
Food and Drug Administration
15800 Crabbs Branch Way
(HFG-3)
Suite 200
Rockville, MD 20855
(301) 427-1934
(301) 427-1935 fax
email: combination@fda.gov

CPC COMBINATION PRODUCTS COALITION

Survey Scope & Methodology

- Focused questions on:
  - Demographics
  - Satisfaction with existing guidance (FDA and non-FDA)
  - Topics on which more or better FDA guidance is needed
- Disseminated widely among industry
- Asked companies to complete only one survey, but to collaborate with their colleagues

CPC COMBINATION PRODUCTS COALITION

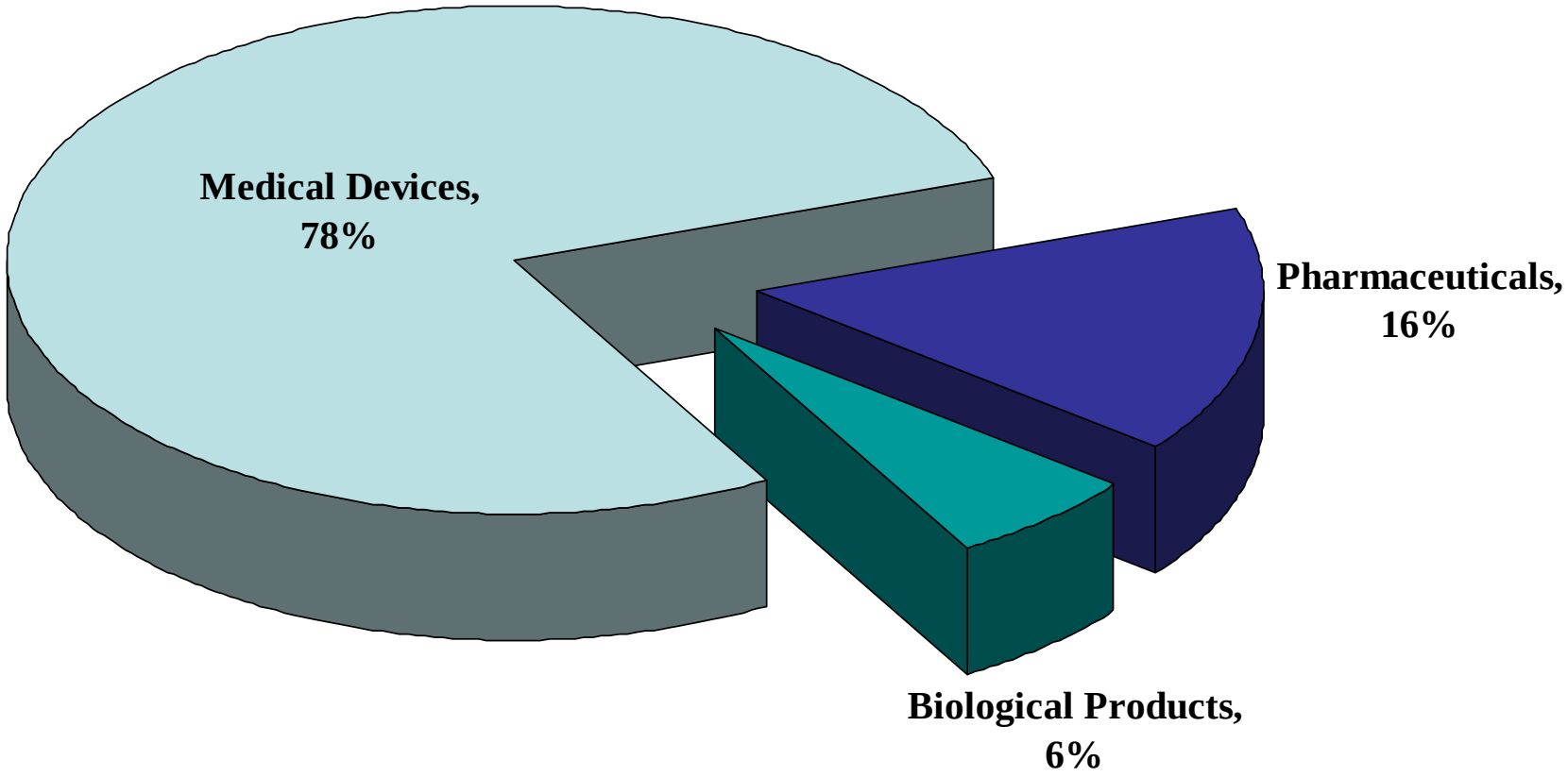
Survey Methodology

- Disseminated widely to the combination products industry
  - Our individual contacts and through trade groups and publications
  - Many thanks to the organizations that helped get the word out:
    - California Healthcare Institute
    - IMDMC
    - *MD&DI*
    - MDMA
    - *MX*
    - NEMA
    - PharmaMedDevice
    - RAPS

- Respondents completed survey via an Internet link that allowed them to remain anonymous (providing identifying information was optional)
- Asked companies to complete only one survey, but to collaborate with their colleagues

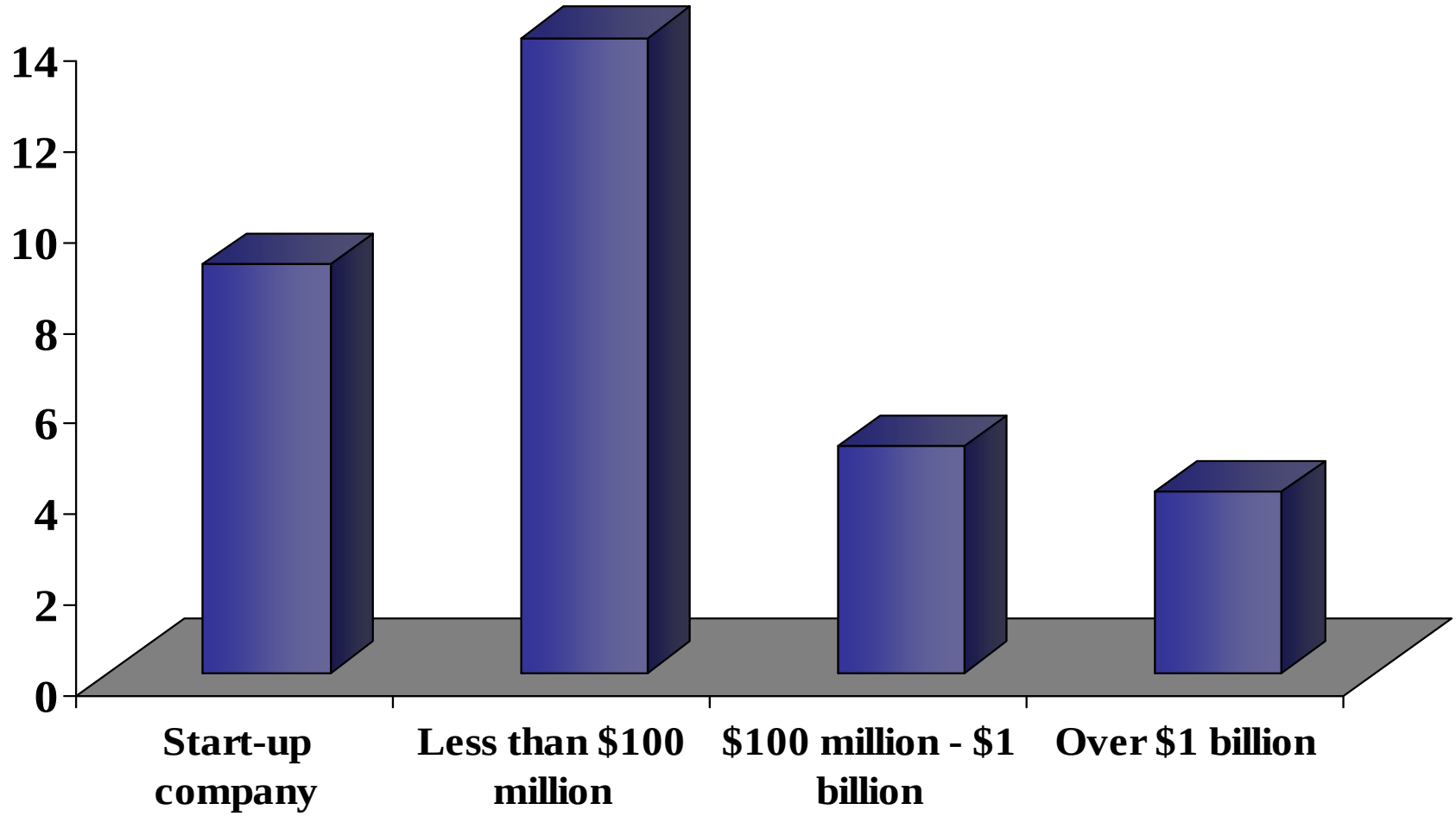
CPC COMBINATION PRODUCTS COALITION

Primary Product Focus



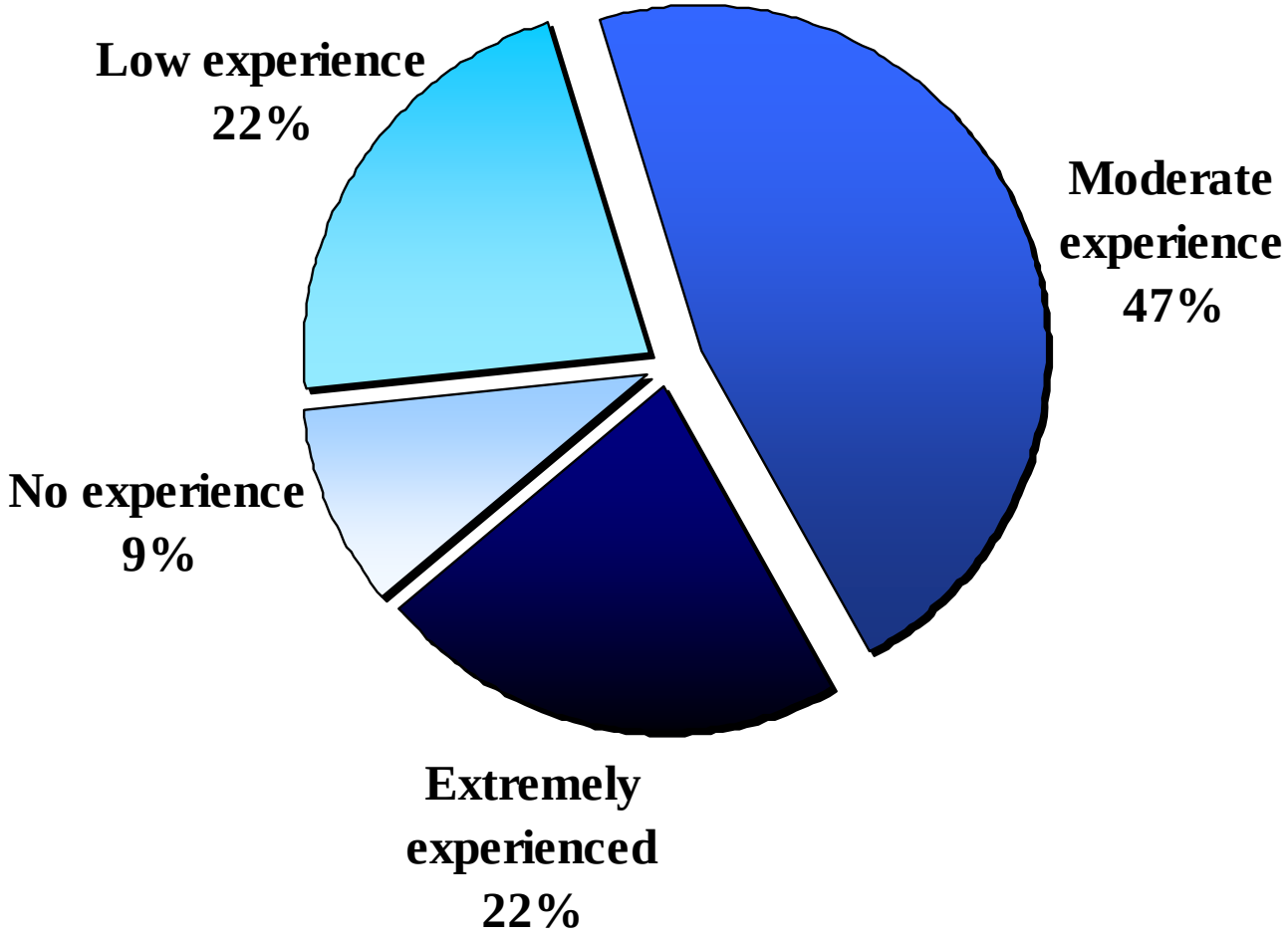
CPC COMBINATION PRODUCTS COALITION

Annual U.S. Sales of Combination Products



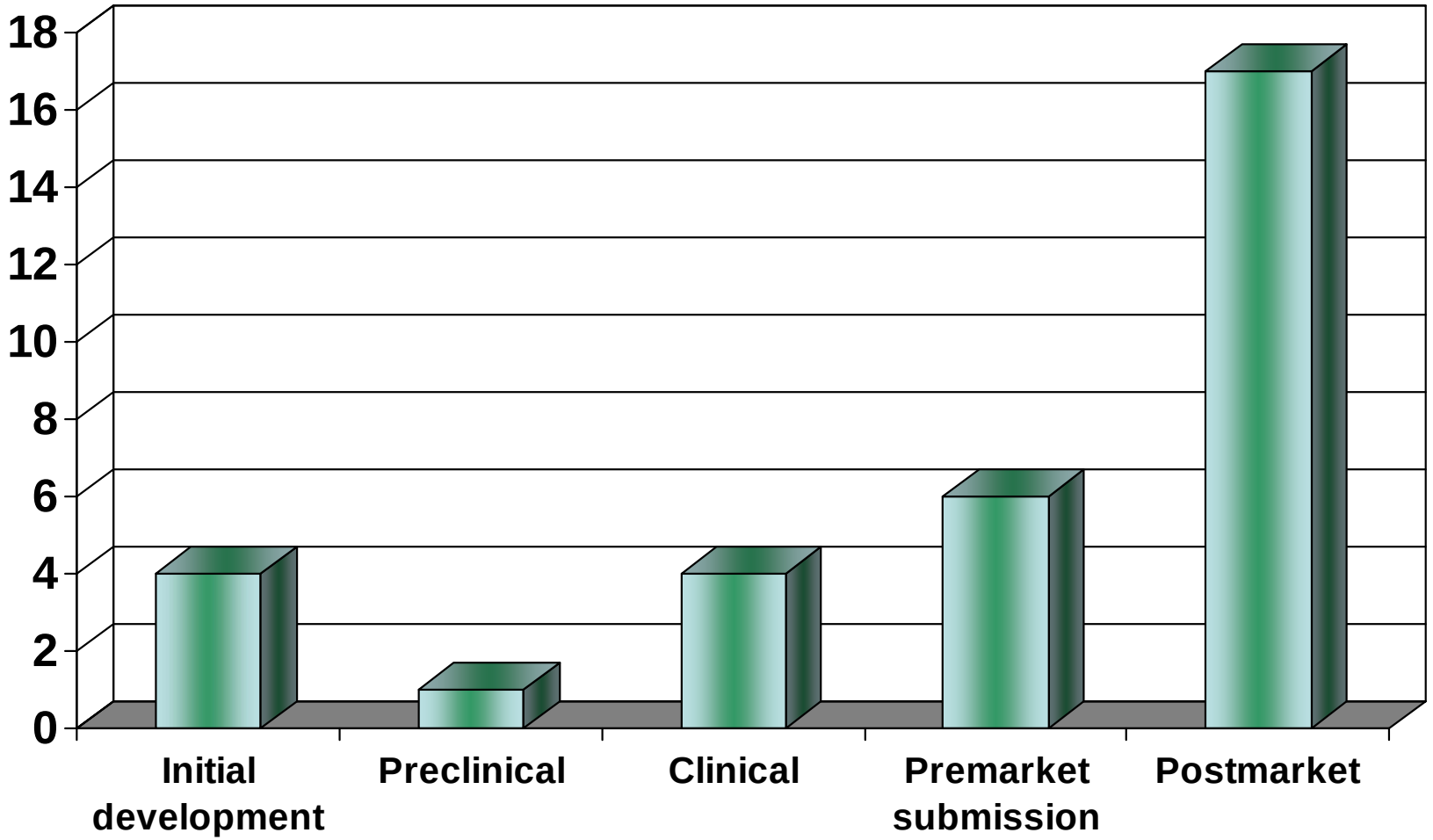
CPC COMBINATION PRODUCTS COALITION

Level of experience with developing and commercializing combination products



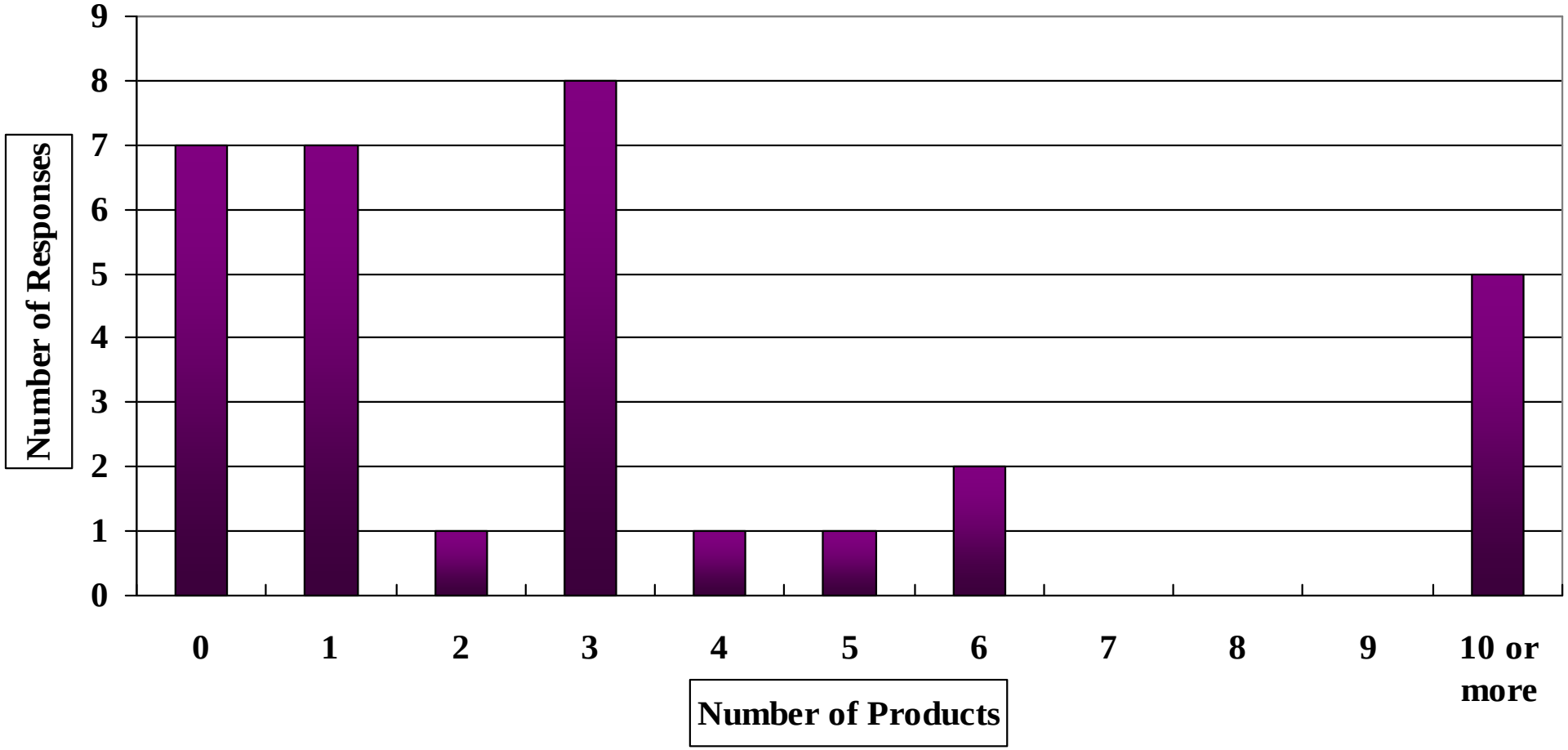
CPC COMBINATION PRODUCTS COALITION

Stage of development of combination product that is furthest along



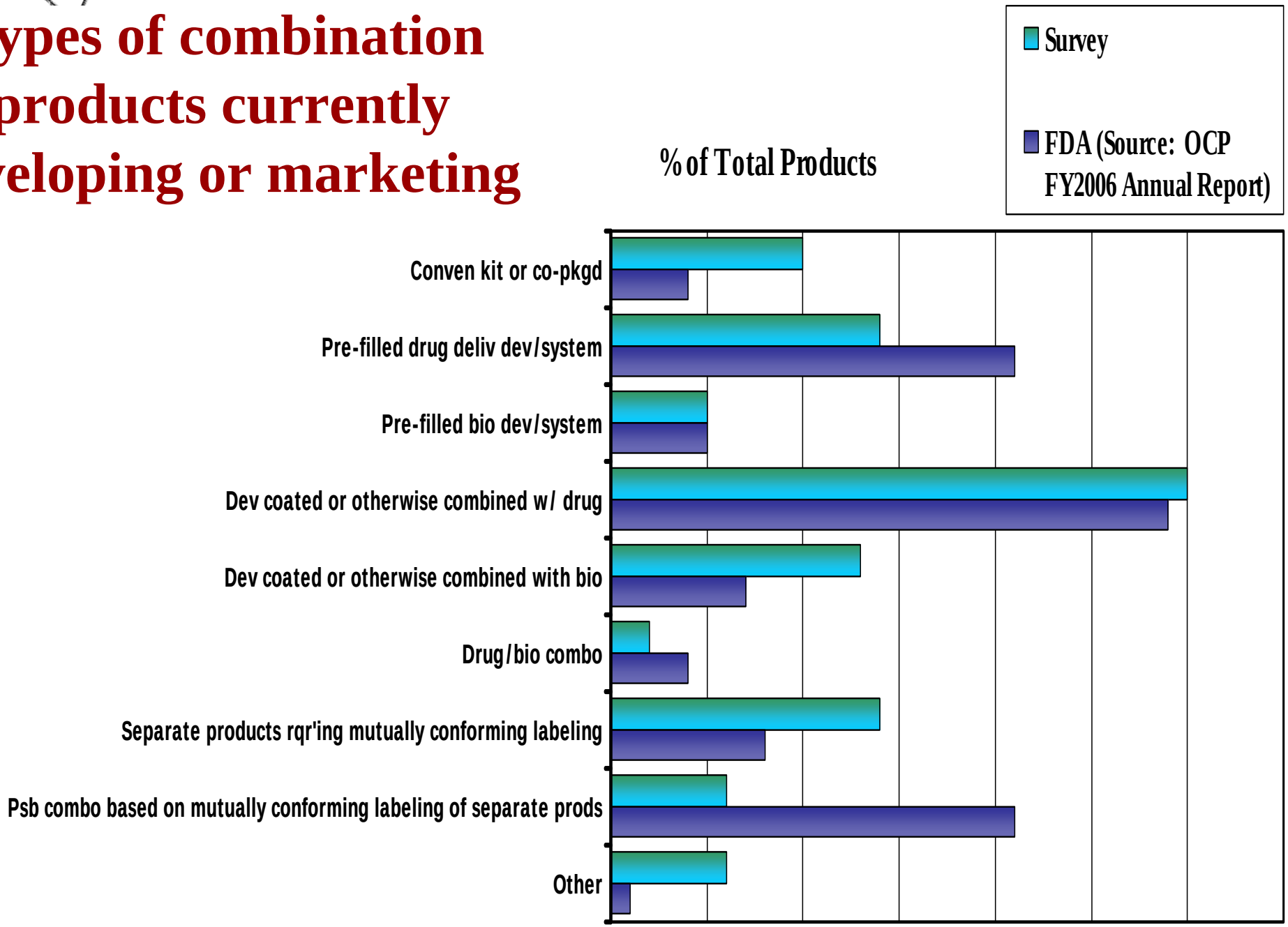
CPC COMBINATION PRODUCTS COALITION

Number of products developed and brought to market



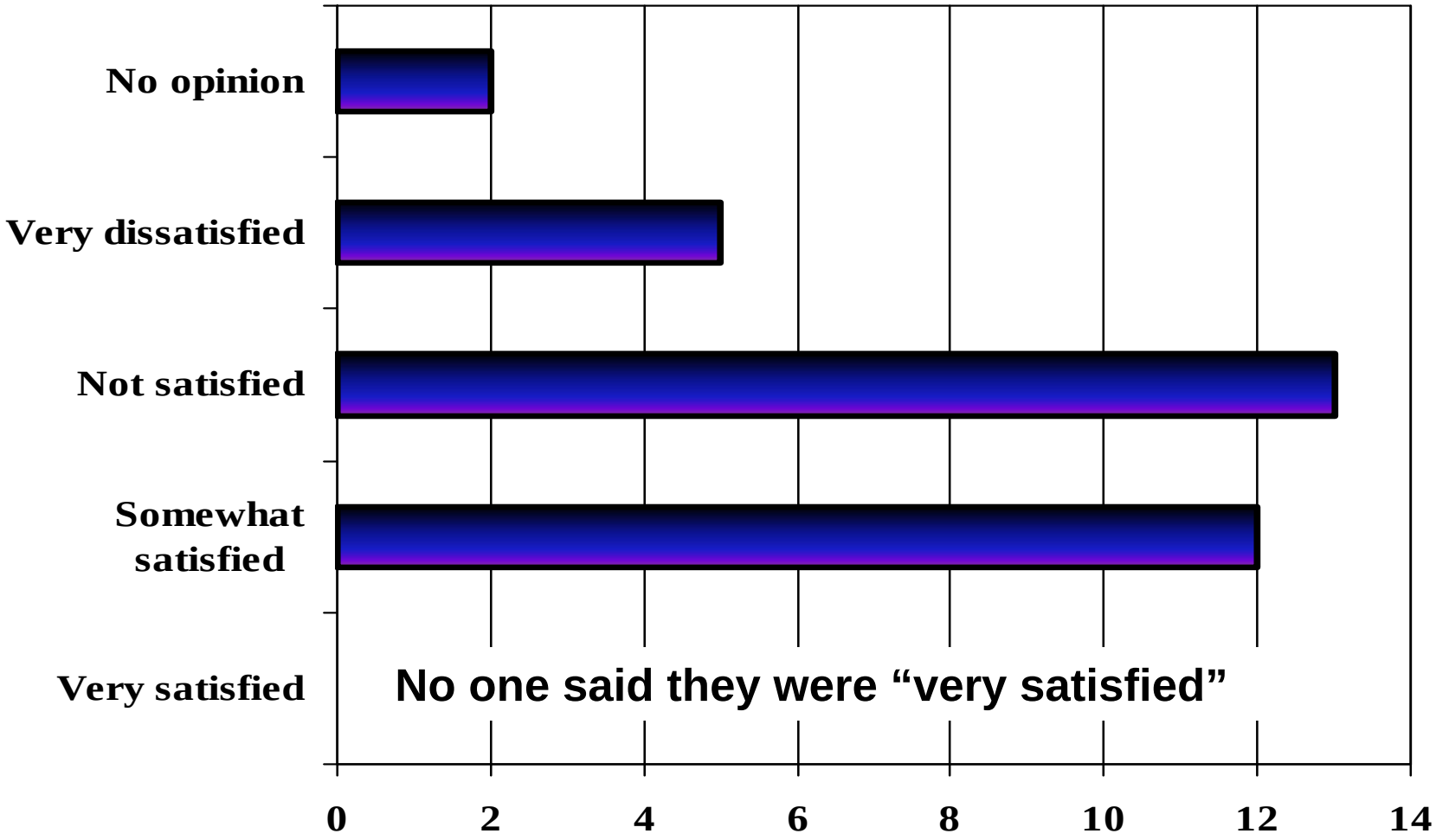
CPC COMBINATION PRODUCTS COALITION

Types of combination products currently developing or marketing



CPC COMBINATION PRODUCTS COALITION

Level of satisfaction with existing guidance (FDA and non-FDA)



CPC COMBINATION PRODUCTS COALITION

Selected Comments on Satisfaction*

Part of the problem with existing guidance documents is that they are at the 40,000 foot level, and there needs to be more detailed regulatory guidance at the 10,000 foot level.

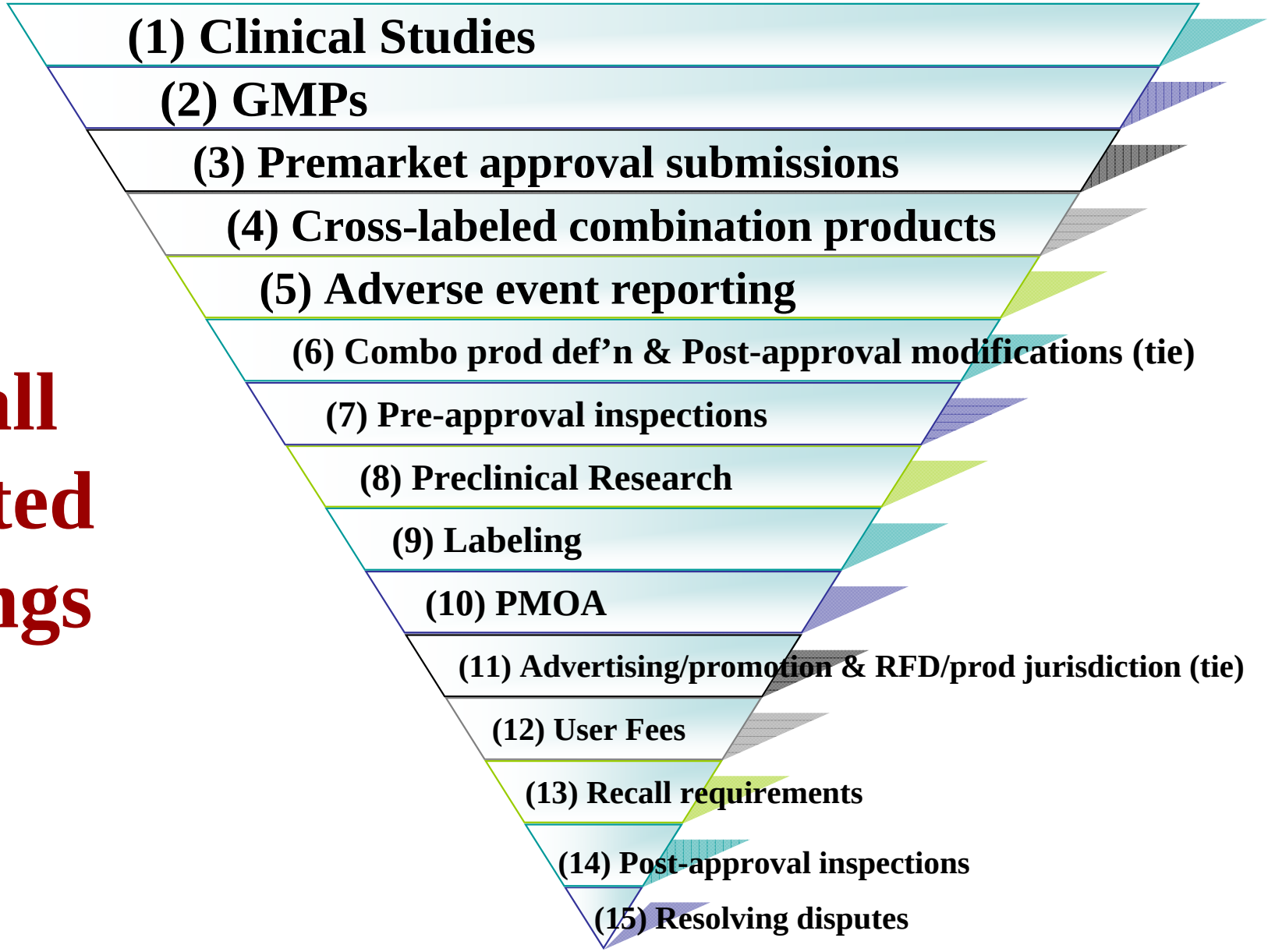
FDA should specify in detail [applicable] pharmaceutical requirements, especially for efficacy, quality, and safety.

The commercial application of a device (which is meant to be modified and continually improved) and a drug/biologic (which is meant to stay the same) is leading to horrific change control on the device side . . . .

*Comments edited for clarity

CPC COMBINATION PRODUCTS COALITION

Overall Weighted Rankings



CPC COMBINATION PRODUCTS COALITION

Topic

1. Who we are
2. Public health importance of combo products
3. The industry's needs for guidance
4. **GMP Proposed Rule**
5. Post-market Safety Reporting Proposed Rule
6. Priorities going forward

CPC COMBINATION PRODUCTS COALITION

GMP Proposed Rule

- Its publication allows enables important public dialogue
- Substantively similar to 2004 draft guidance
  - Each constituent part retains its regulatory status, even after being combined with another part
  - Streamlined or “hybrid” approach for single entity or co-packaged products
  - Implementing guidance will be extremely important

CPC COMBINATION PRODUCTS COALITION

GMP Comment Meeting with FDA and RAPS

- Will take place during comment period (exact date TBD)
- Will focus on pre-written case studies
- Will be in person (DC/Maryland area) and virtual
- If you are interested, let me know so I can add you to our mailing list

CPC COMBINATION PRODUCTS COALITION

Questions/Potential Ambiguities

- Trigger for combined system (proposed 4.4(d))
  - Two or more constituent parts
    - "have arrived at the same facility" OR
    - "manufacture … is proceeding at the same facility"
  - Is this clear? For example, why the need for the second (production) trigger if arrival is sufficient?
  - What about large facilities with unrelated drug and device operations?

CPC COMBINATION PRODUCTS COALITION

Additional Trigger Issue

- Proposed rule defines a constituent part to include any device that is part of a combination product
- Definition of a device includes include components
- Dilemma:
  - constituent parts arriving at a facility or being manufacturing at the facility could be device components, which are traditionally exempt from GMPs,
  - but the proposed rule suggests they need to be made under GMPs

CPC COMBINATION PRODUCTS COALITION

Impact on autoinjectors/products with container closures

- Similar to device component issue described above
- Application of design controls throughout product life cycle? Even when a container closure?
- Clarify that container closures will remain treated as drug components

CPC COMBINATION PRODUCTS COALITION

Combination products with only one constituent part

- Other part is created in situ (e.g., a device that creates a drug)
- Is the manufacture of the product subject only to the GMPs applicable to the part that is manufactured and distributed to user?

Application to biological products

- May need more detailed information
- For example, the proposed rule flags specific differences between drug and device GMPs, but not specific differences as between biological and other GMPs
- Also the container closure issue

CPC COMBINATION PRODUCTS COALITION

Implementation issues

- Timing and substance of the "coordinating guidance"
  - Will be very important
  - Ideally will be published before final rule
- Impact analysis
  - Estimated hours required to comply (25 hours per product) seems very low
  - Time extension for compliance needed?
- Responsibility for compliance oversight
  - Centers? OCP?
  - Communication among agency personnel
  - Field investigator guidance

CPC COMBINATION PRODUCTS COALITION

Topic

1. Who we are
2. Public health importance of combo products
3. The industry's needs for guidance
4. GMP Proposed Rule
5. **Post-market Safety Reporting Proposed Rule**
6. Priorities going forward

CPC COMBINATION PRODUCTS COALITION

Adverse Event Proposed Rule

- As with GMP rule, content is similar to past agency commentary (Concept Paper)
- Again, publication itself enables important dialogue
- Same basic concept as GMP
  - Manufacturer follows a single set of adverse event reporting rules
  - Graft on the portions of other rules that are different
  - Five general areas where rules are different
- New requirement – Constituent part manufacturer reporting an adverse event to manufacturer of companion constituent part or to FDA

CPC COMBINATION PRODUCTS COALITION

Questions/Potential Ambiguities

- Constituent parts with multiple clearances or approvals
  - E.g., cleared device (1) incorporated into a combo product approved under an NDA, but also (2) separately marketed
  - Need for device manufacturer to also file a report?
- Reconciling overlapping reporting requirements
  - Criteria for drug v. device reportable event are very different
  - Default to most demanding?

CPC COMBINATION PRODUCTS COALITION

Assumption that reports always the same type as lead Center

- May not always be the case
- E.g., CDER tells a manufacturer it needs a 510(k), which leads to MDRs
- Where to file?
- If lead Center reviews AEs for all constituents, how will expertise be assured?

CPC COMBINATION PRODUCTS COALITION

Issues with constituent parts

- Reporting an adverse event to manufacturer of companion constituent part or to FDA
  - Is the timeframe – 5 days – reasonable?
  - How will this be monitored/enforced?
- Determining which constituent part is associated with an adverse event
  - Not much detail in the proposed rule
- Line between a component v. constituent part
  - As with GMP, when are device components subject to the rules?

CPC COMBINATION PRODUCTS COALITION

Implementation issues

- Agency IT challenges
- Company IT challenges
  - Heavily automated systems
  - Is 180 days sufficient to delay effectiveness?

CPC COMBINATION PRODUCTS COALITION

Topic

1. Who we are
2. Public health importance of combo products
3. The industry's needs for guidance
4. GMP Proposed Rule
5. Post-market Safety Reporting Proposed Rule
6. **Priorities going forward**

CPC COMBINATION PRODUCTS COALITION

CPC Position on Priorities

Top priorities

- Immediate:
  - GMPs applicable to combination products
  - Post-marketing safety reporting
- Longer-term:
  - Transparency and the need for guidance
  - Clinical trials on combination products
  - Post-approval product modification issues

CPC COMBINATION PRODUCTS COALITION

Needed Transparency

1. **Embracing** the idea that the agency can freely communicate with the public before and during the guidance development process outside the formal notice and comment mechanism.
2. **Producing** more guidance.
3. **Adopting** procedures designed to ensure that the content of guidance addresses the public's key questions.
4. **Responding** to comments.
5. **Finalizing** draft guidance.
6. **Employing** metrics designed to track the agency's progress in guidance development.
7. **Continuing** to avoid using speeches, warning letters and other such communications to announce new policy that should be in guidance.
8. **Investing** more time in planning guidance development.

CPC COMBINATION PRODUCTS COALITION

Ways to Get Involved

- Companies interested in CPC should visit: **www.combinationproducts.com**
  - Membership structure
  - Policy Positions
- Active LinkedIn group (you don't need to be a member to join)
- Outreach such as free wiki experiment for drafting injector comment

CPC COMBINATION PRODUCTS COALITION

Questions?